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EARLY, LOCAL TREATMENT OF DIPHTHERIA.

BY

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Early, Local Treatment of Diphtheria.

Diphtheria begins as a local disease. It is said that the membrane is found most frequently on the tonsils and less frequently on the posterior wall of the pharynx. From these parts the disease may extend upwards or downwards.

In some cases, the membrane spreads with great rapidity, and, in order to prevent the multiplication of the bacilli locally, and thus avoid the absorption of their toxic products, which alone invade the general system to any extent, it is important to lose no time in applying treatment in the early stages of the disease. It is not a question of days but of hours, and, where the local manifestations are accessible, the means used should be able to destroy the bacilli after a contact of a few seconds. According to Welch & Abbott of Baltimore,* the bacilli are not found in the mucous membrane, but chiefly in the deeper layers of the diphtheritic membrane. To reach them, it is obviously necessary to do something more than apply a germicide to the diphtheritic deposit. It must be applied in and underneath the fibrinous membrane, which must be broken

*Etiology of Diphtheria, by Professor W. H. Welch and A. C. Abbott, M. D., Bulletin of the Johns Hopkins Hospital, Vol. II, No. 11, 1891.

up and disintegrated in order that the germicide may reach all parts of it. There are many agents that will kill the bacilli after reaching them, but few that can render the more exceptional service of breaking up and penetrating the diphtheritic deposit. In the laboratory, corrosive sublimate, acids, chlorine and other substances, will quickly kill the bacilli, but they do not disintegrate the membrane, and, therefore, to simply apply most antiseptics to its surface is like trying to smoke out a woodchuck by means of a fire near his hole. Further, some antiseptics are poisonous, and, when applied in spray or in gargle, more reaches the friend than the enemy.

Peroxide of hydrogen is a remedy which is not poisonous, and has been much used in diphtheria. It has usually been employed in a 15-volume solution diluted with water, and, in many cases, dilution with several parts of water is directed. The full 15-volume solution, however, is not sufficient to kill the bacilli promptly, and I shall show later that, instead of diluting the 15-volume solution, it is necessary to use one that is much stronger. The chemical formula of peroxide of hydrogen is H_2O_2; when decomposed, it splits up into O and H_2O, and its use in medicine depends upon the fact that this decomposition is easily brought about. We have thus at our command a very convenient form for employing nascent oxygen. I need not enlarge upon the obvious advantages of such an agent; in it we have a remedy that is harmless, is a germicide, and has many other uses. It is an oxydizing agent of the best possible nature, as it treats living tissue kindly, while at the same time, its animosity, if I may use the term, is such against various forms of decayed organic matter and dead tissue that its oxygen is liberated and the dead mass attacked by the full fury of nascent oxygen.

At the beginning of my last service at the Boston City Hospital, I asked myself whether this valuable agent, peroxide of hydrogen, could not be used in sufficient concentration,—*First*, to kill the bacilli within a few seconds; *Second*, to do this without harm to the patient. These conditions fulfilled it would be necessary only, *Third*, to find the means of bringing the peroxide to the vital point; and *Fourth*, to preserve the solution.

In carrying on this investigation, I have had the interest and valuable assistance of Dr. H. P. Talbot of the Massachusetts Institute of Technology who made and tested the strong solutions for me, and devoted much careful study to their analysis.

The commercial solution of peroxide of hydrogen, of about 20 volumes strength, and acid reaction was concentrated by distillation over a water-bath in a partial vacuum. During the distillation the decomposition is apparently very small, at least, until the solution has reached a strength of from 250 to 300 volumes. The concentration may be continued to a strength at which the solution will evolve with permanganate of potassium 500 times its volume of oxygen. At this point, the solution begins to decompose rapidly.

The strength of the peroxide of hydrogen solution is not estimated in the same way in all countries. In America, for instance, a 15-volume solution is one that when mixed with permanganate of potassium, under suitable conditions, will evolve fifteen times its own volume of oxygen. One-half of this oxygen comes from the peroxide and the other half from the permanganate. In other countries, in estimating the strength of the solution, the amount of oxygen evolved from the peroxide of hydrogen only is considered. In this paper the American way is used. Six and one-third volumes represent 1 per cent. of peroxide of hydrogen. A 20-volume solution, for example, would, therefore, contain 3 per cent. of peroxide of hydrogen. It would avoid confusion and simplify the matter to give up the method of designating the strength of peroxide of hydrogen by volume and speak only of the *percentage* of peroxide of hydrogen in the solution.

On the bacteriological side, Mr. G. V. McLauthlin, of the same institution, has most kindly made a series of tests, with control experiments, upon the action of various substances, chiefly different strengths of peroxide, upon the bacillus of diphtheria. I quote the following from his account of the process:

"In any of the ordinary methods for determination of the germicidal action of any liquid disinfectant upon a given bacterial species, three distinct and successive processes may usually be recognized. These are: first, the mingling for a known period of a pure culture of the given species with a suitable amount of the germicide; second, the dilution, after the desired interval has elapsed, of this mixture to the extent necessary not only to check further bactericidal action but also to avoid the possibility of any future inhibitory effect; and third, the planting of a portion of this dilution in a suitable culture medium, in order to permit the growth and consequent recognition of any bacteria which may have survived the action of the germicide.

As a source of the diphtheria bacillus we used a pure culture that came originally from the laboratory of Dr. Welch of Johns Hopkins University. From this, plantings were made in bouillon,

and to insure greater accuracy, in most of the experiments old and fresh bouillon cultures were used side by side, or a mixture of the two was employed. All tests given in the tables were made in duplicate.

The following record of a single action experiment with its control will serve to illustrate this method.

5 c.c. of acid 50-volume (8%) peroxide solution were placed in a 60 c.c. Erlenmeyer flask and 0.25 c.c. added of a bouillon culture of the diphtheria bacillus. Ten seconds after, in order to stop the action of the peroxide, the mixture was quickly poured into a litre flask containing 600 c.c. of slightly alkaline normal salt solution. Thirty seconds after this, the whole having been well shaken, 0.2 c.c. were transferred to 75 c.c. of alkaline normal salt solution in another flask. At the end of three minutes, 1 c.c. of the last dilution was planted in 6 c.c. of bouillon. At the end of four and a half minutes 1 c.c. of the dilution was added to 6 c.c. of melted glycerine agar at 40° C., and the mixture at once poured into a Petri dish.

In the control experiment, 0.25 c.c. of the bouillon culture of the bacillus were mixed with 600 c.c. of alkaline normal salt solution, *then* 5 c.c. of acid 50-volume (8%) peroxide added, and all well shaken. Thirty seconds after the addition of the peroxide, 0.2 c.c. of the mixture were transferred to 75 c.c. of alkaline normal salt solution in another flask. After four and a half minutes, a glycerine agar plate was made as before.

After a few days' growth in the incubator, the agar plate, from the control experiment, showed 158 colonies of the diphtheria bacillus. At the same time, neither the agar plate, nor the bouillon tube, prepared from the action experiment, showed any growth.

Evidently the agar plate is of especial advantage when a part only of the bacteria are killed, i.e., when the germicide is diluted just beyond its effective limit. The bouillon tube gives no precise means of distinguishing between the survival of a part and the survival of the whole of the bacteria."

I found that a 50-volume (8%) acid solution of peroxide of hydrogen was a more efficient germicide than a 50-volume (8%) solution of peroxide alone. In other words, the value of the peroxide solutions was much increased by the presence of a small amount of acid, and for this reason acid solutions of peroxide should be employed. Alkaline solutions do not keep as well and are less effective as germicides.

In Table I, No. 1 will be found an analysis of the peroxide solution which I have used.

TABLE I.

EXPERIMENTS ON THE ACTION OF PEROXIDE OF HYDROGEN AND CERTAIN ACIDS UPON THE DIPHTHERIA BACILLUS.

Action Period, 10 Seconds.

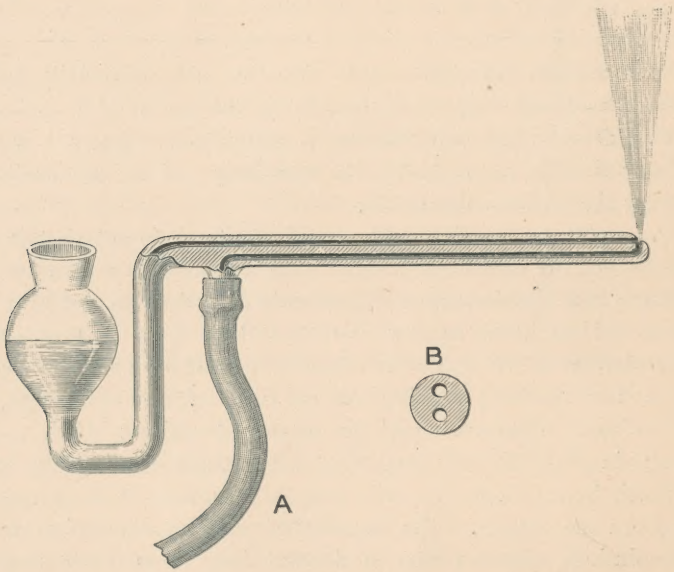
GERMICIDE.	Strength necessary for complete disinfection in 10 seconds when 0.5 c.c. of bouillon culture are added to 10 c.c. of the germicide.
1. Hydrogen Peroxide of usual acidity, i.e., with about .25% H_2SiF_6, .75 % H_2SO_4, and traces of HCl.,etc.,per 1 c.c. of 100-vol.(16%) peroxide.	Between 25 and 50 volumes (4 and 8%).
2. Hydrogen Peroxide slightly acid, but nearly neutral.	Between 100 and 150 volumes (16 and 24%).
3. Sulphuric Acid.	½ to 1%.
4. Hydrofluosilicic Acid.	" "
5. Hydrochloric Acid.	" "

It is evident from this table that the acids, especially hydrofluosilicic acid, are important factors in the germicidal action of the peroxide solutions, but, besides its germicidal property, it will be seen later that the peroxide has the necessary and unique quality of rendering the bacillus accessible.

In regard to my first and second points, I found that in the laboratory all the bacilli were killed after ten seconds contact with a 50-volume (8%) acid solution of peroxide of hydrogen, and that this solution did no harm to the tissues, and as a rule, caused little inconvenience to the patient. Solutions containing 100 volumes (16%) caused smarting, which continued from one to two minutes, but even stronger solutions could be employed without injury to the tissues; in fact, the mucous membrane seems to bear the solution much better than the skin, probably because it is so quickly diluted on the former. The amount of pain or discomfort which these solutions cause, seems to depend less upon their strength than upon the local conditions and upon the individual. Even stronger solutions than the 100 volume (16%) may be used, but they cause more pain, and are only necessary in cases where the membrane is very tough and thick. The strength of the solutions to be used must depend, therefore, upon what we wish to accomplish. To cleanse the throat merely, and as a gargle, a solution rather stronger than 15 volumes (2.4%) will answer, but, where the membrane is thick and tough, it is necessary to use a solution of from 50

to 200 volumes (8 to 32%) in order to have it efficient. As soon as the peroxide touches the dead tissues it begins to decompose into oxygen and water. During this action the membrane is attacked and disintegrated, and the way is thus opened for the germicidal action of the peroxide and the substances associated with it. But in this very decomposition the strength of the solution is reduced, and therefore to compensate for this loss we must use a stronger solution than would be necessary in the laboratory.

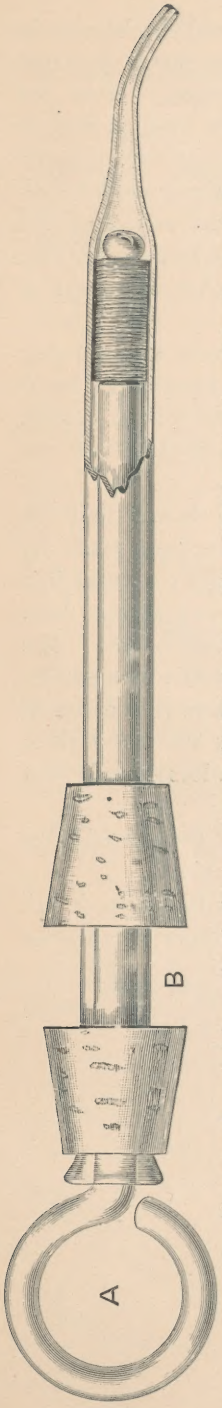
Third, let us now consider the means used to make the applications. They are chiefly a special atomizer and a special syringe. In order to reach all parts of the throat it has been necessary to change the tips of the atomizers so as to throw the spray in these different directions — straight, up, down, right and left. This is inconvenient to both physician and patient, and to simplify the matter I have designed a glass atomizer, a drawing of which is here given.



A is rubber tubing to hand-bulb. The cut is one-half size except the section ofthe tube at B, which is full size. The bulb in the drawing should have more the shape of a top, and when of such shape it can be placed on its side without losing any of its contents if it is not more than half full.

By means of this atomizer the spray may be sent in three directions, up and right and left, in the throat without taking it out of the mouth, but merely by turning it in the hand.

Made by P. J. McElroy, East Cambridge, Mass., U. S. A., who manufactures various forms of glass atomizers out of this double-bored glass tubing of his invention.



The syringe is one inch longer than the drawing, otherwise this is the full size. The walls of the syringe beyond the piston are thick, and the tip is smooth, having been rounded in a flame.

The special syringe,* a drawing of which is here given, is of my own make, and although of glass it has not yet been broken. The form is such that it can reach any part of the throat within sight. The syringe is first filled with a strong solution of peroxide. It is held in one hand, the thumb being placed in the ring, A, while the first and second fingers grasp the body of the syringe at B, between the two corks. The mouth of the patient is opened, the tongue depressed with a spoon or depressor, the point of the syringe pushed through the membrane and a few drops of the solution pressed out. Immediately there appears a frothy swelling and the patient expectorates a white froth. The membrane then in some cases looks swollen, white and thickened, and it is not until about an hour later that the most marked improvement is apparent. The amount of discomfort caused depends to a certain extent on the part to which the application is made. Touching the back of the pharynx always causes gagging, while, on the contrary, the tonsils are sometimes very tolerant, and the point of the syringe may be thrust into the boggy swollen tissue for a large fraction of an inch, ¼ to ½.

As regards the frequency of the application of the germicide I can give no rule that applies to all cases. The problem is to treat early, to disintegrate and clear off the membrane by means of the spray and syringe. In the syringe a 100 (16%) or, more often, a 200-volume (32%) solution should be used, applications being made, of a few drops each, into and underneath the membrane wherever needed. This should be done from one to three times daily for the first day or two, after

*I have tried Dr. Seibert's syringe with fresh chlorine water, but have had too little experience with his method to express an opinion.

which the spray alone may suffice. The spray should also be used in 50 (8%) or 100-volume (16%) strength, once in four hours, although it may be desirable to use it oftener in some cases. Where the membrane yields readily to the spray this may be used at first to clean away as much as possible of it, and the remainder may be cleared by the syringe. The treatment to be effective must be energetic and well carried out in the early days. Besides treating the membrane locally, it is well to use antiseptic prophylactic treatment in the pharyngeal and nasal regions, such as douches or sprays of peroxide solution and diluted chlorine water.

In applying this treatment it is important to have a good light; a kerosene lamp with a parabolic reflector like a locomotive headlight is good, but by day I prefer to place the patient's head in such a position that when the mouth is opened the back of the throat has direct daylight upon it.

Fourthly, from the literature of the subject, I feared that the peroxide solutions would prove very unstable. The tests made by Dr. Talbot show that 44.6-volume (7%) solutions keep six weeks in a temperature of from 70° to 80° Fahr. without suffering serious loss. In a cool, dark place or a refrigerator they keep ~~even~~ better. The 100-volume (16%) solutions will keep for a few days in a temperature of from 70° to 80° Fahr., and in a refrigerator 24 days with a loss of only 6 ~~per cent.~~ The 200-volume (32%) solutions are less stable; they will keep for six days in a refrigerator with a loss of only ~~four per cent.~~

The result of some of the tests made with the peroxide of hydrogen solutions is given on the next page, in Table II.

Fresh chlorine water has also been tested and found to deteriorate much more rapidly than the peroxide solutions which have been used.

TABLE II.

CHANGES IN PEROXIDE OF HYDROGEN SOLUTIONS OF DIFFERENT STRENGTHS WHEN KEPT IN THE LIGHT AT 70° TO 80° FAHR.

ORIGINAL STRENGTH.	APPROXIMATE ACIDITY.	TIME OF STANDING.	FINAL STRENGTH. Volumes.	Percentages.
19.4 volumes. 3.08%.	0.2%	3 days.	19.4	3.08
		7 "	19.2	3.05
		13 "	19.2	3.05
44.6 " 7.08%.	0.5%	3 days.	44.6	7.08
		7 "	43.5	6.90
		13 "	43.	6.82
		43 "	40.4	6.41
100.3 " 15.92%.	1.%	3 days.	100.3	15.92
		14 "	83.	13.17
		21 "	76.	12.06
202. " 32.06%.	2.%	3 days.	188.	29.84
		14 "	130.	20.63
		21 "	105.	16.66
51.5 " 8.17%.	Distinctly acid to litmus paper.	1 day.	51.	8.09
		4 days.	51.	8.09
		28 "	45.	7.14
41. " 6.50%.	Less acid than the one above.	2 days.	41.	6.50
		30 "	32.	5.08
51. " 8.09%.	Acidity very slight, less than the one above.	1 day.	50.	7.93
		31 days.	5.4	0.85
34.4 " 5.46%.	Slightly alkaline with caustic potash.	2 days.	9.1	1.44
		8 "	1.8	0.28
28.9 " 4.59%.	Slightly alkaline with ammonia.	2 days.	0.6	0.09
		8 "	0.0	0.00

CHANGES WHEN KEPT IN REFRIGERATOR.

	Acidity.			
101. volumes. 16.03%.	1.%	3 days.	99.4	15.77
		6 "	98.6	15.65
		17 "	96.1	15.25
		24 "	95.	15.08
202. " 32.06%.	2.%	3 days.	201.6	32.00
		6 "	194.4	30.86
		17 "	181.	28.73
		24 "	170.	26.98
300. " 47.62%.	3.%	9 days.	274.	43.49
		12 "	271.	43.01
		26 "	251.	39.84
		33 "	240.	38.09
390. " 61.90%.	4.%	13 days.	336.	53.33
		19 "	332.	52.69
		30 "	310.	49.21
		37 "	290.	46.03

Was 1 day at 70° to 80° Fahr.

The amount of the strong solutions required for a patient is not large, as the treatment has to be continued for a few days only. The strong solutions should not be allowed to come in contact with the skin, as they are irritating, nor with colored fabrics or the hair, as peroxide is a bleaching agent.

The following cases illustrate the use of the peroxide. In the first case, the patient, an adult, had a chill. The next evening, when first seen, there was only a very small patch on one tonsil, too little in the opinion of the physician who saw her on which to base a diagnosis. Within a few hours this increased rapidly, and when I first saw the patient membranes were to be seen covering both tonsils, the posterior pillars, the posterior side of the uvula, and there were some spots on the pharyngeal wall, all tenacious, and not to be removed by the forceps. I made local applications of the peroxide with the spray and syringe; the membranes did not spread. The treatment was continued locally for five days, and the patient made a quick recovery, was able to be out of bed within a week, and there were no after effects. As in this case, there had been exposure to diphtheria, it would have been wise to use the peroxide from the moment suspicion was aroused.

The second case is especially instructive. In this, as it happened, both tonsils had been removed a few weeks before; their site was now covered with a membrane white on the edges, but dirty and necrotic in character over a considerable area. After the application of a 50-volume (8%) solution of peroxide every four hours for thirty hours, the membrane was reduced to a thin film. Then the treatment was not given for ten hours, and, at the end of this time, the membrane had re-covered the original area and spread on to the posterior pillars and behind, on the left side, tending to become septic in character. The peroxide was again applied every four hours, after which the membrane did not spread. On the seventh day thereafter the throat was practically clear, and on the eighth day the patient sat up.

The position of the membrane in the 32 medical cases that recovered was as follows:

Nine cases on the tonsils only; 23 cases on the tonsils and other parts. These cases all had the peroxide treatment. The patients made good recoveries, and there was a notable absence of after effects. No case that came early to the hospital died.

Germicides such as chlorine water, corrosive sublimate, acids, peroxide of hydrogen, chloroform, or mixtures of certain of them, are still under investigation.

In behalf of the early, local treatment of diphtheria, it should be stated that the membrane is generally accessible in the beginning.

The foregoing is a brief outline of two months crowded hospital service, on the medical side of the diphtheria ward, and is offered as a contribution towards the early local treatment of diphtheria.